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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,645	07/23/2003	Claudio Pisano	4865-74	6903

23117 7590 09/03/2008
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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1612	
MAIL DATE	DELIVERY MODE
09/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/624,645	PISANO ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-78 and 86-106* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-78 86-106* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 6-5-08 is acknowledged.

Claims included in the prosecution are 71-78 and 86-106.

Contrary to applicant's indication that claims 71-78 and 86-105 are present in the application, claims 71-78 and 86-106 are present in the application and therefore, 71-78 and 86-106 are included in the prosecution.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 71-78 and 86-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al in combination with Allen (6,056,973), Burke (5,552,156), in further combination with Stracher (5,008,288).

Wang et al disclose cationic liposome compositions containing claimed alky acyl carnitine esters for gene delivery. The fatty acid groups are oleyl or myristoyl, palmitoyl or stearoyl groups. The liposomes contain helper lipid (DOPC), cholesterol. The liposomes are administered intravenously (abstract, Scheme 1 on page 2208, Tables 3 and 4 on page 2211, page 2214, col. 2).

What is lacking in Wang et al is the teaching of the use of claimed drugs such as anti-cancer drugs, camptothecins in particular.

Allen teaches that liposomes are delivery agents for anticancer drugs such as camptothecin derivatives and genes (abstract, col. 16, lines 10-17).

Burke teaches that liposome stabilize camptothecin derivatives (abstract, examples and claims).

Stracher teaches that because of the presence of carnitine or its derivatives as part of liposomal structure, the drug containing liposomes will be delivered in much greater amounts to the desired target organs and much less is metabolized by the liver (abstract, col. 17, line 51 through col. 18, line 44).

It would have been obvious to one of ordinary skill in the art to use the liposomes of Wang et al to delver drugs other than genes, such as anti-cancer drugs or cosmetic agents with a reasonable expectation of success since liposomes are known drug and cosmetic agent carriers and as evident from Allen, the term drug encompasses genes and anti-cancer agents such as camptothecin derivatives and liposomes are carriers for both genes and anti-cancer agents. One of ordinary skill in the art would use camptothecin derivatives as drugs since they are known to be encapsulated in liposomes because of stabilization by liposomes as taught by Burke. One of ordinary skill in the art would be motivated to use carnitine derivatives containing liposomes of Wang et al for the delivery of camptothecin derivatives of Burk since Stracher teaches the advantages of the presence of carnitine derivatives in liposomal structure in the drug delivery.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant argues the following regarding Wang:

> "Wang et al. refer to liposomes prepared from carnitine derivatives, which efficiently complex with DNA and transfer the DNA complex into cells and in mice (page 2201 2nd column). In particular, liposomes interact with DNA resulting in a change in the membrane properties of the liposome and compaction of DNA, leading to the formation of a tightly packed DNA - lipid complex which must assemble and disassemble during the transfection process. This complex is influenced by the transition temperature of the lipids, which plays an important role during the introduction of DNA into cells, after the complex is internalized (see page 2208 column. 1- 2, page 2212 column 1). Wang et al. disclose the compounds defined as 4a, 4b, 4c, 4d, 4e and 4f (scheme 1 page 2208), chosen for gene delivery. Wang et al teach that the compounds 4a-f alone have good transfection efficiency only when a helper lipid is present (emphasis added) in the formulation, and the in vitro transfection activity of the alkyl acyl carnitine esters follows the order of 4d > 4e > 4b > 4f > 4c > 4a (page 2211 2nd column). It will be noted that the most efficient liposome of Wang has both C 14 alkyl/acyl chains. In the order of efficiency, the following rank is given by Wang et al. (alkyl/acyl chain) C14 > C12 > C18/C18(9) > C16 > C18. Wang et al. address their study only to liposomes that can be filled in with DNA in order to efficiently transfect in into cells and are completely silent on drug delivery. The liposomes of Wang et al. have the characteristic (transition temperature of lipids) that are needed for forming stable complexes with DNA which are capable to assembly and disassembly during transfection. According to the present invention, the liposome is efficient in delivering taxol or camptothecin to lung tumor with no need of a helper lipid and the efficiency is not linked to chain length. In the working example, page 55 and following of the specification, the liposome has no helper lipids and the alkyl/acyl chain is C11/C16. It will be noted that C11 alkyl is not provided by Wang et al., and C 16 acyl ranks very low in Wang efficiency test."

These arguments are not persuasive. Instant claim language does not exclude the helper lipid taught by Wang. With regard to the efficiency linked to the chain length in Wang and not linked to chain length in instant invention, the examiner points out that instant claims do not recite this limitation. With regard to applicant's arguments that there is no teaching of drug in Wang, the examiner points out that the secondary reference of Allen teaches the equivalency between the anti-cancer drugs genes for liposomal encapsulation.

Applicant argues that Allen discloses liposome composition comprising preformed liposomes and does not disclose esters of L-carnitine made liposomes, which entrap taxol or camptothecin. This argument is not persuasive since Allen is combined for its teachings of the use of liposomes for the delivery of both genes and camptothecins. Therefore, it would have been obvious to one of ordinary skill in the art to use Wang's liposomes for the delivery of even camptothecin since Allen teaches the use of liposomes for the delivery of either of these agents.

Applicant argues that Burke overcomes the problems of insolubility and instability of camptothecin drugs administered in their free from by providing that the lactone of the camptothecin drugs administered in their free form by providing that the lactone of the camptothecin structure is intercalated in the bilayer of the liposome so that the ring is protected from hydrolysis and that the liposomes are phospholipids and not carnitine. This argument is not persuasive. First of all, instant claim language does not exclude phospholipids. Secondly, since camptothecin being hydrophobic, one would expect its incorporation into the liposomal bilayer and obtain similar stability since Wang's

liposomes contain even a phospholipid. With regard to applicant's argument that Burke does not teach instant carnitine, and silent on drug delivery and organ targeting, the examiner points out that Burke is combined with Wang which teaches the carnitine derivative and Allen is teaches the use of liposomes for drug delivery and organ targeting. Applicant argues that in Stracher L-carnitine is only taught to be selective carrier for a drug specific to cardiac and skeletal muscle and no indication is given that an ester of an alkanoyl L-carnitine can be employed to prepare a cationic liposome for selective delivery to target organs for antitumor drugs such as camptothecin and taxol. This argument is not persuasive since instant claims do not exclude cardiac and skeletal muscles and applicant has not shown any unexpected results by using a carnitine derivative instead of carnitine or other carnitine derivatives taught by Stracher.

3. Claims 86-106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hsu (5,653,996) in combination with Wang et al cited above.

Hsu discloses liposomal compositions for the delivery of therapeutic or cosmetic agents. The agents include plasmids (DNA), a variety of passenger molecules. The compositions can be administered topically (col. 4, lines 53-55, col. 6, line 10 through col. 8, line 1, col. 14, lines 52-56, col. 15, lines 1-9).

What is lacking in Hsu is the teaching of the inclusion of claimed carnitine derivatives.

Wang as discussed above teaches the ability of the claimed carnitine derivatives to form liposomes by themselves or in combination with other bilayer forming phospholipids (abstract).

It would have been obvious to one of ordinary skill in the art to use the liposomes of Wang in the teachings of Hsu for the delivery of therapeutic as well as cosmetic agents with a reasonable expectation of success since both Wang and Hsu are directed to liposomes and liposomes are carriers of active agents.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments regarding Wang have already been addressed by the examiner. Applicant argues that Hsu is a general disclosure relating to liposomes, which can be made by phospholipids and others for the delivery of active agents, and Hsu does not specifically disclose a carnitine/acyl L-carnitine made liposomes for selective delivery of taxol or camptothecin. This argument is not persuasive. Hsu also teaches genes and other therapeutic agents. Hsu in particular teaches on col. 7, lines 41-42 teaches tumoricidal agents, though not specifically taxol and camptothecins. Applicant has not shown any unexpected results obtained by using the claimed tumoricidal agents namely taxol and camptothecins.

4. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore, Ph.D/
Primary Examiner, Art Unit 1612

GSK